



SYSTEMATIC REVIEW

Zika virus infection as a cause of congenital brain abnormalities and Guillain-Barré syndrome: From systematic review to living systematic review [version 1; referees: 2 approved, 1 approved with reservations]

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Abstract

Background. The Zika virus (ZIKV) outbreak in the Americas has caused international concern due to neurological sequelae linked to the infection, such as microcephaly and Guillain-Barré syndrome (GBS). The World Health Organization stated that there is “sufficient evidence to conclude that Zika virus is a cause of congenital abnormalities and is a trigger of GBS”. This conclusion was based on a systematic review of the evidence published until 30.05.2016. Since then, the body of evidence has grown substantially, leading to this update of that systematic review with new evidence published from 30.05.2016 – 18.01.2017, update 1.

Methods. We review evidence on the causal link between ZIKV infection and adverse congenital outcomes and the causal link between ZIKV infection and GBS or immune-mediated thrombocytopenia purpura. We also describe the transition of the review into a living systematic review, a review that is continually updated.



Results. Between 30.05.2016 and 18.01.2017, we identified 2413 publications, of which 101 publications were included. The evidence added in this update confirms the conclusion of a causal association between ZIKV and adverse congenital outcomes. New findings expand the evidence base in the dimensions of biological plausibility, strength of association, animal experiments and specificity. For GBS, the body of evidence has grown during the search period for update 1, but only for dimensions that were already populated in the previous version. There is still a limited understanding of the biological pathways that potentially cause the occurrence of autoimmune disease following ZIKV infection.

Conclusions. This systematic review confirms previous conclusions that ZIKV is a cause of congenital abnormalities, including microcephaly, and is a trigger of GBS. The transition to living systematic review techniques and methodology provides a proof of concept for the use of these methods to synthesise evidence about an emerging pathogen such as ZIKV.

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Zika virus, causality, living systematic review, congenital abnormalities, Guillain-Barre syndrome, microcephaly

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Introduction

Outbreaks of Zika virus (ZIKV) infection in the Americas have caused international concern owing to the severity of neurological sequelae linked to the infection ([WHO statement IHR 2005](#)). During 2016, the number of countries affected by the ZIKV outbreak had grown from 33 countries ([WHO situation report 05.02.2016](#)) to 75 countries ([WHO situation report 05.01.2017](#)). By March 9, 2017, 31 countries had reported microcephaly or other congenital central nervous system (CNS) abnormalities potentially associated with ZIKV infection and 23 had reported an increase in the incidence of the immune-mediated condition Guillain-Barré syndrome (GBS) or laboratory confirmed ZIKV in persons with GBS ([WHO situation report 10.03.2017](#)). The causal association between ZIKV and adverse neurological outcomes has now been examined in many systematic and non-systematic reviews of research^{1,2}. Case reports of other conditions in people with ZIKV infection, including immune-mediated idiopathic thrombocytopenia purpura (ITP), have also been published³⁻⁶.

The World Health Organization (WHO) based its assessment, that there is “sufficient evidence to conclude that Zika virus is a cause of congenital abnormalities and is a trigger of GBS” ([WHO Zika causality statement](#)), on a review of systematically identified studies up to May 30, 2016 and nonsystematically identified studies up to July 29, 2016⁷. The review addressed specific questions about 10 dimensions of causal associations, based on the work of Bradford Hill⁸ and organised as a causality framework ([Supplementary Table 1](#)) that covers: temporality (cause precedes effect); biological plausibility of proposed biological mechanisms; strength of association; exclusion of alternative explanations; cessation (reversal of an effect by experimental removal of, or observed decline in, the exposure); dose-response relationship; experimental evidence from animal studies; analogous cause-and-effect relationships found in other diseases; specificity of the effect; and the consistency of findings across different study types, populations and times. The review included 108 articles about congenital abnormalities or GBS but there was no, or insufficient evidence to answer questions in several dimensions of the causality framework⁷. The causality framework included questions about ITP, but the review authors judged the number of published articles to be too low to assess causality. Since the WHO statement and accompanying publication, about 200 scientific publications every month are added to the body of evidence about all aspects of research about ZIKV.

A living systematic review would help to overcome some of the challenges of keeping up to date with the high volume of ZIKV research publications. A living systematic review is a systematic review that is “continually updated, incorporating relevant new evidence as it becomes available”⁹, which can help in fields where evidence is emerging rapidly and where new review outcomes might change policy or practice decision¹⁰. Technical solutions are available to facilitate the reviewing process, such as automated searching and deduplication and computer-assisted screening of article titles and abstracts, increase the efficiency and speed

of a review team and transform the review into a living document.

This article aims to fulfil two separate objectives. First, we update our systematic review⁷ with new evidence published from May 30, 2016 to January 18, 2017 about all 10 dimensions of the causal associations between ZIKV and (a) congenital brain abnormalities, including microcephaly, in the fetuses and offspring of pregnant women and (b) GBS/ITP in any population. Second, we describe the transition of the review into a living systematic review.

Methods

Classic protocol

We performed the review according to the protocol registered in PROSPERO CRD42016036693 ([PROSPERO protocol](#)). The eligibility criteria, information sources and search strategy, study selection and data extraction are the same as reported in the protocol and in the previous publication⁷. In brief, the search covers PubMed, Embase and LILACS electronic databases; the Pan American Health Organization (PAHO), WHO, the Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC) websites; and several preprint databases (BioRxiv, PeerJ and ArXiv). Search terms included ‘Zika virus’ and ‘ZIKV’ and corresponding MESH terms. Two reviewers screen and select articles for inclusion and extract data independently. We included publications that held information on at least one of the ten dimensions of the causality framework, regardless of the study design⁷. We gathered publications systematically from May 30, 2016 to January 18, 2017 for this update. We refer to the previous version of the review as the baseline review⁷ and to this current update as update 1. Reporting of the results follows the Preferred Reporting Items of Systematic reviews and Meta-Analyses (PRISMA) statement ([Supplementary File 1](#))¹¹.

From systematic review to living systematic review

To keep up with the quantity of published research, we developed a living systematic review workflow ([Supplementary File 2](#)). We have identified three modules that could be automated ([Figure 1](#)). As of December 2017, module 1, searching and deduplication, and part of module 3, the output of the report have been automated. Reviewers can be notified daily with a list of new unique search results so that screening can be performed rapidly. Following manual data extraction and synthesis, the output can be updated semi-automatically. We use the online database Research Electronic Data Capture (REDCap)¹² to maintain the references, perform screening and extract data into piloted extraction forms. We plan to update the review twice per year with formal peer reviewed updates ([Figure 2](#)), and continually through a web platform.

We synthesised the findings as narrative summaries of the evidence according to causality dimension and outcome, as previously described⁷, and compare them with the the baseline review. We use the term ‘confirmation’ to summarise findings of new studies included in update 1 if they report the same findings

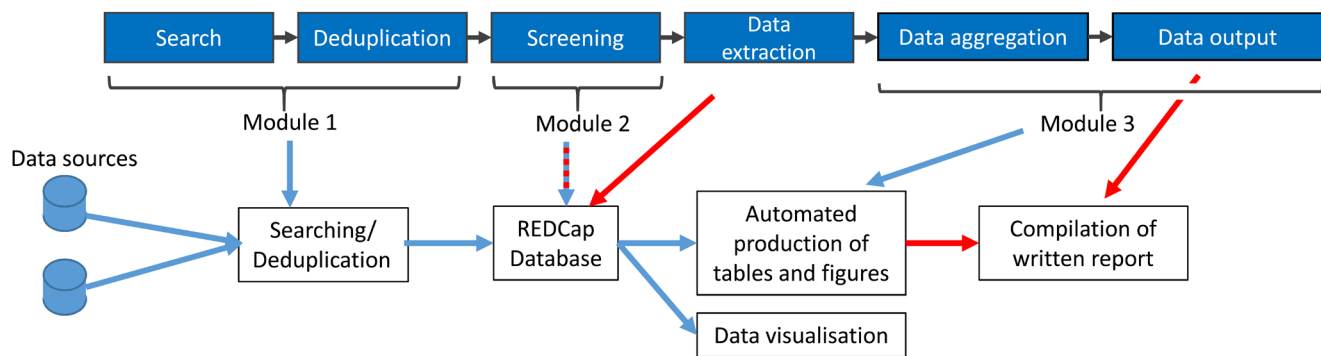


Figure 1. Living systematic review automation. Blue boxes and arrows represent the conceptual steps in a systematic review process. Automation is divided in three modules. Module 1 is the automation of the searching and deduplication of information from different data sources. Module 2 partly automates screening. Module 3 automates the production of tables and figures and outputs the data to a web platform (Data visualisation). Blue arrows represent automated information flows; red arrows represent manual input. The blue-red dashes arrow represents a blended form where reviewers verify automated decisions of the system. The white boxes show the practical implementation of the system and the data flow.

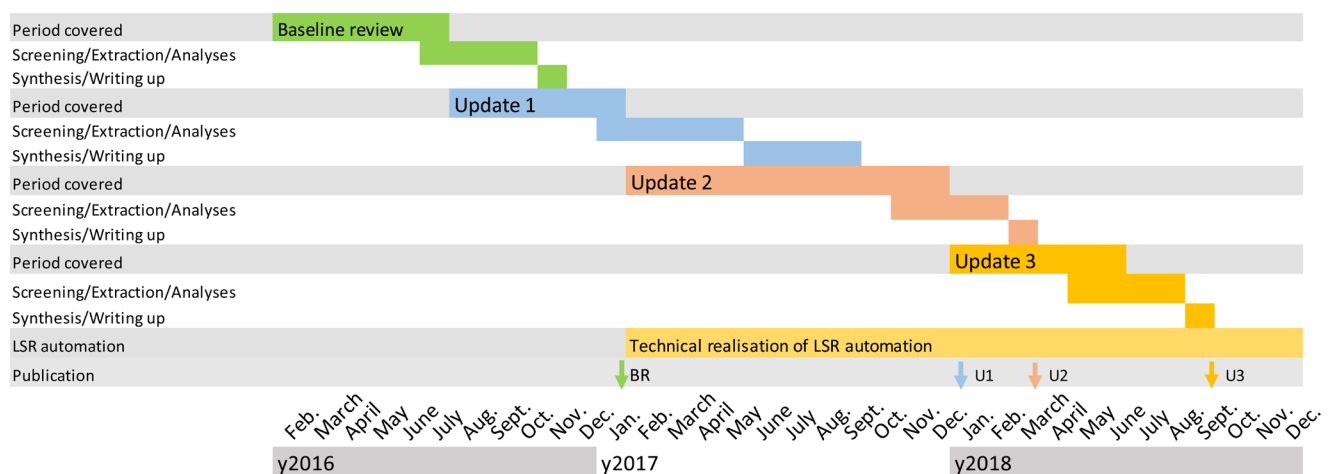


Figure 2. Timeline of review conduct, publication and transition to a living systematic review. The baseline review (BR,⁷) and Update 1 (U1) this version classic, manual systematic review. During 2017 automation of the workflow was conducted resulting in a projected Update 2 (U2) and 3 (U3) with more rapid throughput. LSR, living systematic review.

as those in the baseline review. We use the term ‘expansion’ of evidence if studies included in update 1 provide new findings.

Results

Between May 30, 2016 and January 18, 2017, we identified 2413 publications. After deduplication, we retained 1699 unique records. Based on screening of title and abstract, we discarded 1025 publications, retaining 674 items; after screening of the full text, 101 publications were included. **Figure 3** shows the PRISMA flow diagram for this review¹¹. Seventy-seven publications held information on one or more dimensions of the causality framework on adverse congenital outcomes and 25 on GBS or idiopathic thrombocytopenia purpura. **Table 1** compares the included publications, study types and the causality dimension(s) they address in the baseline review⁷ and update 1 of the review.

Adverse congenital outcomes

A detailed overview of the new evidence is provided in **Table 2** and **Supplementary Table 2**. In the search period for review

update 1, an additional 548 cases of adverse congenital outcomes were described in 32 studies^{12–43}. Adverse congenital outcomes described were: clinical microcephaly^{12–17,20–24,26–31,33,35,37,40–42}, imaging confirmed brain abnormalities^{12,15,17,19–24,26–31,35,37,38,40,42}, intrauterine growth restriction^{15,17,31,38,40,42}, ocular disorders^{12,17,27–29,31,38,40} and auditory disorders^{12,18,29}.

Temporality. This update confirms the previous conclusion that ZIKV infection precedes the adverse congenital outcomes. We found an additional 21 publications in which ZIKV infection preceded the adverse congenital outcome at an individual level^{12,15–18,26–31,35–40,42,44,45} and at a population level^{45,46}. Infections in the first and second trimester seemed to be related to the most adverse outcomes^{31,40}. Cohort studies of pregnant women from French Guiana and Brazil found a higher proportion of congenital abnormalities in babies born from mothers infected in the first and the second trimester^{31,40}.

Biological plausibility. This update includes an additional 42 studies^{14,17,23,24,32–36,38,39,42,47–76}, some of which expand the

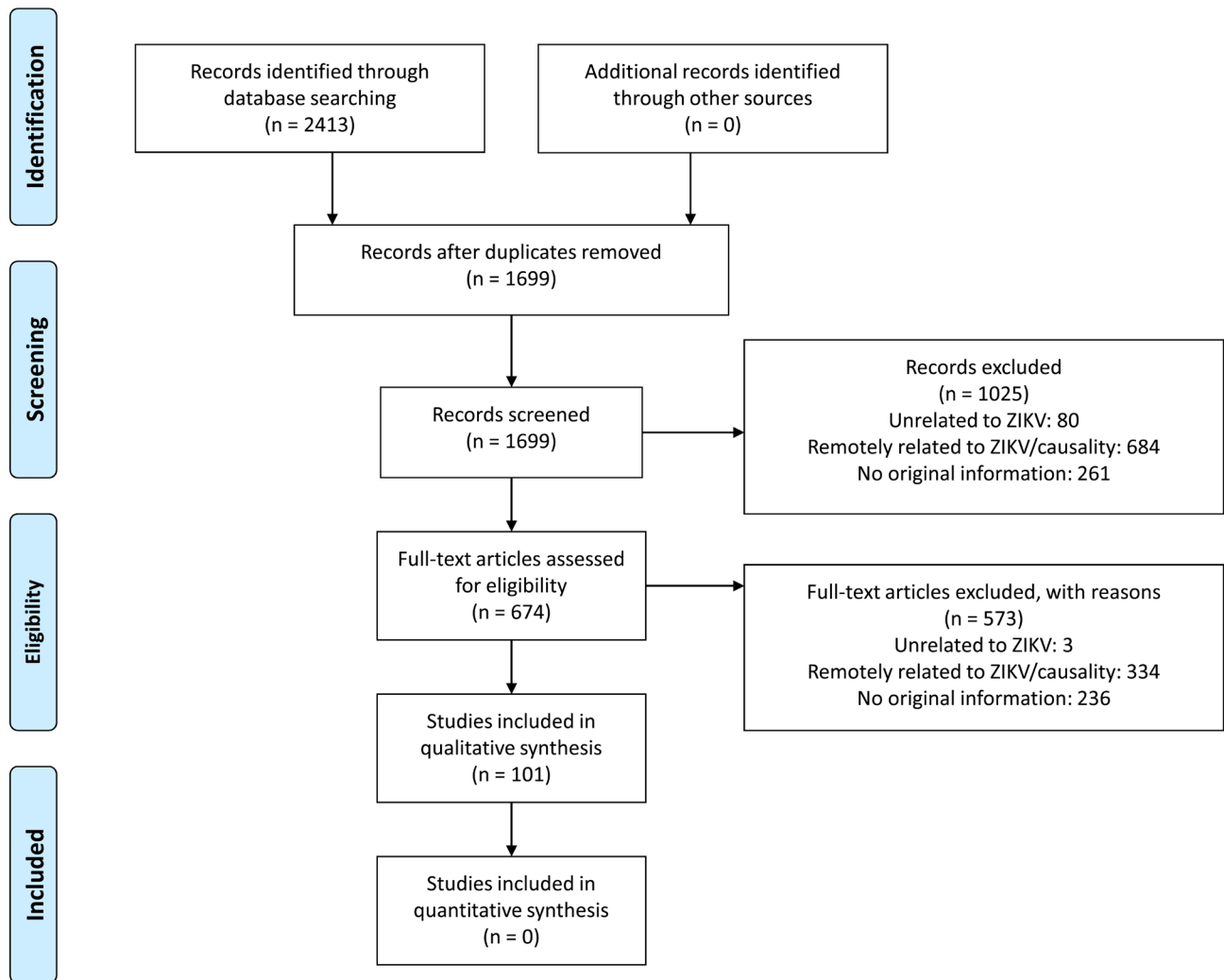


Figure 3. PRISMA flow diagram of included studies.

evidence base. Whereas in the baseline review, we found inconclusive evidence of whether ZIKV particles in infants were capable of replication, both *in vivo* and *ex vivo* studies now demonstrate that this is the case^{33,36,47,50,53-55}. Furthermore, there was a strong expansion of the evidence clarifying how ZIKV causes adverse congenital outcomes. ZIKV uses receptors from the TAM family to enter cells⁴⁷⁻⁵², where the virus induces cell death, primarily in developing neuronal cells^{60,61,64,65,67,69,70,75}.

Strength of association. We included five publications that confirm a strong association between ZIKV infection and adverse congenital outcomes^{21,22,31,40,41}. The strength of association at an individual level was high but imprecise, owing to small sample sizes. Estimates from cohort studies^{31,40} appeared to be lower than those from case-control studies^{21,22,41}. The definition of the outcomes and the outcomes assessed, varied between studies. The risk of any adverse congenital outcomes was higher and more variable than the risk of microcephaly. The risk ratio for microcephaly between ZIKV unexposed and exposed was

4.4 (95% CI: 0.2-80.8) in a cohort in Brazil³¹ and 6.6 (95% CI: 0.8-56.4) in a cohort in French Guiana⁴⁰. In the Brazilian cohort³¹, the proportion of any adverse congenital outcomes among ZIKV infected women was high (41.9% [49/117]), compared with the uninfected group (5.2% [3/57]). In a prospective case-control study in Brazil, women with laboratory-confirmed ZIKV had 55.5 (95% CI: 8.6-infinity) times the odds of having a baby with microcephaly compared with women without evidence of ZIKV infection²¹. A retrospective case-control study in Hawaii found an odds ratio of 11.0 (95% CI: 0.8-147.9)⁴¹. In the latter, however, exposure was assessed retrospectively using serology.

Exclusion of alternatives. We included 23 new studies in this update^{12,14,17-19,21-28,30,31,34,36-38,40,42,45,77}. Many studies included in this review that reported on adverse outcomes of congenital ZIKV excluded TORCH infections^{12,14,17-19,21-28,30,31,34,36-38,40,42,45,77}; exposure to toxic chemicals^{12,14,18,23,28} or genetic conditions^{12,18,23,28,30,36,42}. Maternal or foetal malnutrition, hypoxic-ischaemic lesions and

Table 1. Summary of included publications by study type and on which causality dimension they provide evidence. One publication can address multiple causality dimensions. Comparison between the current (U1) and the baseline review (BR, 7) stratified by outcome. GBS/ITP, adverse autoimmune outcomes (Guillain Barré syndrome/idiopathic thrombocytopaenia purpura). NA, not applicable; evidence about analogous conditions was not searched systematically; the dimension of consistency used information in items included for all other causality dimensions.

| Condition and version | Adverse congenital outcomes | | GBS/ITP | |
|---------------------------------------|-----------------------------|-----------|-----------|-----------|
| | BR, N | U1, N | BR, N | U1, N |
| Study type | | | | |
| Case report | 9 | 13 | 9 | 5 |
| Case series | 22 | 12 | 5 | 11 |
| Case-control study | 0 | 3 | 1 | 1 |
| Cohort study | 1 | 8 | 0 | 0 |
| Cross-sectional study | 2 | 1 | 0 | 1 |
| Controlled trials | 0 | 0 | 0 | 0 |
| Ecological study/outbreak report | 5 | 4 | 19 | 7 |
| Modelling study | 2 | 0 | 0 | 0 |
| Animal experiment | 18 | 8 | 0 | 0 |
| In vitro experiment | 10 | 22 | 0 | 0 |
| Sequencing and phylogenetics | 3 | 3 | 2 | 0 |
| Biochemical/protein structure studies | NA | 3 | NA | 0 |
| Total: | 72 | 77 | 36 | 25 |
| Causality dimensions | | | | |
| Temporality | 21 | 21 | 26 | 21 |
| Biological plausibility | 25 | 42 | 4 | 0 |
| Strength of association | 3 | 5 | 2 | 4 |
| Alternative explanation | 18 | 23 | 6 | 11 |
| Cessation | 2 | 0 | 6 | 2 |
| Dose-response relationship | 0 | 0 | 0 | 0 |
| Experiment | 20 | 11 | 0 | 0 |
| Analogy | NA | NA | NA | NA |
| Specificity | 0 | 1 | 0 | 0 |
| Consistency | NA | NA | NA | NA |

underlying genetic conditions were not excluded. No single alternative explanation could be given to explain the relation between ZIKV and adverse congenital outcomes.

Cessation. We did not find any new publications for this causality dimension. Evidence is still lacking on the effect of intentional removal due to lack of vaccination or elimination of mosquitoes on a large scale.

Dose-response. There is still no direct evidence about the association between Zika viral load and probability of adverse congenital outcome in observational studies, or of an association between symptomatic status and outcome. In a study in the United States, Honein *et al.* found similar proportions of adverse congenital outcomes in symptomatic and asymptomatic ZIKV-infected mothers³².

Animal experiments. This update of the review includes an additional 11 studies^{63,71,78–86}. These studies confirm a consistent relation between a range of contemporary ZIKV and adverse congenital outcomes, including from Brazil⁸⁵, Puerto Rico⁷⁹ and Mexico^{80,81}. The body of evidence coming from animal studies has grown; both in mice and macaques, congenital anomalies such as intra-uterine growth restriction and signs of microcephaly were observed after ZIKV infection^{78,84,85}.

Analogy. As for the baseline review, evidence for this dimension was not reviewed systematically because our search strategy did not include terms for other infections or conditions. Studies included in this version of the review confirm the analogy between congenital ZIKV and TORCH infections⁸⁷. Vertical transmission of West Nile virus and dengue virus were summarised in the baseline review. In update 1, we included a case series

Table 2. Summary of the evidence on the relation between ZIKV infection and adverse congenital outcomes. Evidence is displayed for each dimension and for each question of the causality framework. Zika virus (ZIKV); Dengue virus (DENV); West Nile virus (WNV); Chikungunya virus (CHIKV); Toxoplasmosis, Other [Syphilis, Varicella-zoster, Parvovirus B19], Rubella, Cytomegalovirus, and Herpes infections (TORCH); Central Nervous System (CNS). NA, not applicable; evidence about analogous conditions was not searched systematically; the dimension of consistency used information in items included for all other causality dimensions. the baseline review (BR), update 1 (U1).

| Question | BR, N | U1, N | Summary |
|---------------------------|-------|-------|--|
| Temporality | | | |
| 1.1a | 18 | 19 | Confirmation. Sufficient information to conclude that ZIKV infection precedes the development of congenital abnormalities in individuals ^{12,15-18,26-31,35-38,40,42,44,45} . |
| 1.1b | 2 | 1 | The peak of adverse congenital outcomes in Colombia was 24 weeks after infection ⁴⁵ (similar to Brazil, 34 and 30 weeks ⁷). |
| 1.2 | 18 | 19 | Confirmation. Most mothers of infants with adverse outcomes were exposed to ZIKV during the first or the second trimester of their pregnancy ^{34,94} . Third trimester exposure can lead to brain malformations as well ¹⁹ . |
| Biological plausibility | | | |
| 2.1 | 1 | 6 | Confirmation of the role of viral entry factors (receptor-ligand interaction) ⁴⁷⁻⁵² . |
| 2.2 | 1 | 4 | Substantial expansion of the evidence on which cells express the receptors responsible for cell entry of ZIKV ^{47,50-52} . |
| 2.3 | 11 | 11 | Expansion of evidence, sufficient information to conclude that ZIKV particles can be found in the umbilical cord blood and/or amniotic fluid of previously or currently infected mothers ^{14,23,24,32-36,38,39,42} . |
| 2.4 | 0 | 7 | The evidence that ZIKV particles found in tissue of the offspring are capable of replication was inconclusive in the previous version. In this update we found that <i>in vitro</i> evidence strongly indicates these ZIKV particles are capable of replication ^{47,50,53-55} . <i>Ex vivo</i> experiments demonstrate ZIKV capable of replication as well ^{33,36} . |
| 2.5 | 6 | 7 | Expansion of evidence, sufficient information to conclude that particles can be found in the brain and other tissues of cases with congenital abnormalities ^{14,17,23,24,33,34,56} . |
| 2.6 | 7 | 6 | Confirmation. ZIKV particles found in the brain are capable of replication ^{33,56-60} . |
| 2.7 | 9 | 22 | Strong expansion of evidence; Expansion of the understanding of how ZIKV causes congenital anomalies ^{49,52,54,57,58,60-76} . |
| Strength of association | | | |
| 3.1 | 2 | 5 | Expansion of evidence on the strength of association at an individual level ^{21,22,31,40,41} . However, the estimation of the effect size remains imprecise. |
| 3.2 | 1 | 0 | At a population level, confirmation lacks on the strength of association. However, 29 countries reported a relative increase in microcephaly cases during the ZIKV outbreak (WHO situation report 05.01.2017). |
| Exclusion of alternatives | | | |
| 4.1 | 18 | 23 | Confirmation. In many epidemiological studies TORCH infections are assessed ^{12,14,17-19,21-28,30,31,34,36-38,40,42,45,77} . |
| 4.2 | 4 | 5 | Confirmation. Exposure to toxic chemicals has been excluded ^{12,14,18,23,28} . |
| 4.3 | 0 | 0 | No exclusion of alternative explanation: maternal/foetal malnutrition. |
| 4.4 | 0 | 0 | No exclusion of alternative explanation: hypoxic-ischaemic lesions. |
| 4.5 | 3 | 7 | Confirmation of evidence where the role of genetic conditions was excluded ^{12,18,23,28,30,36,42} . |
| 4.6 | 0 | 0 | No exclusion of alternative explanation: radiation. |
| Cessation | | | |
| 5.1 | 0 | 0 | No publication with evidence that intentional removal of ZIKV infection in individuals leads to a reduction in congenital abnormalities. |
| 5.2 | 0 | 0 | No publication with evidence that intentional removal of ZIKV infection at population-level leads to a reduction of cases of congenital anomalies |
| 5.3 | 2 | 0 | Natural removal (end of epidemic) leads to a reduction in microcephaly cases in Brazil; Other countries have shown a decrease in reported microcephaly cases as the cumulative ZIKV incidence plateaued (http://www.paho.org/hq/index.php?option=com_content&view=article&id=12390&Itemid=42090&lang=en). |
| Dose-response | | | |
| 6.1 | 0 | 0 | No publication with evidence that the risk of adverse congenital outcomes is associated with the viral load in the mother. |
| 6.2 | 0 | 0 | No publication with evidence that the clinical severity of the infection of the mother determines the severity of the congenital anomalies. In one cohort study, symptoms in the mother did not influence the outcome ³² . |

| Question | BR, N | U1, N | Summary |
|--------------------|-------|-------|---|
| Animal experiments | | | |
| 7.1 | 3 | 3 | Expansion of the evidence that the inoculation of pregnant female animals (mice and macaques) with ZIKV causes congenital anomalies in the offspring ^{78,84,85} . |
| 7.2 | 10 | 3 | Confirmation of the evidence that the intracerebral inoculation of newborn mice with ZIKV leads to ZIKV replication in the CNS ^{81,82,86} . |
| 7.3 | 8 | 3 | Expansion of the evidence that other routes of inoculation of newborn animals with ZIKV leads to ZIKV replication in the CNS (intravaginal infection of adult mice, subcutaneous infection of newborn mice) ^{79,80,84} . |
| 7.4 | 1 | 8 | Expansion of the evidence that other experiments with animals or animal-derived cells support the association of ZIKV infection and congenital anomalies ^{63,71,78–83} . |
| Analogy | | | |
| 8.1 | NA | NA | CHIKV was shown to be vertically transmissible and lead to adverse congenital outcomes ⁸⁸ . |
| 8.2 | NA | NA | Confirmation. Congenital ZIKV analogous to other TORCH infections ⁸⁷ . |
| 8.3 | NA | NA | For most analogous pathogens, infections earlier in the pregnancy have a higher risk of adverse outcomes. |
| Specificity | | | |
| 9.1 | 0 | 1 | Expansion of evidence for distinct congenital Zika syndrome. Unique pattern of five features suggested: severe microcephaly with overlapping cranial structures, subcortical location of brain calcifications, macular scarring and retinal mottling, congenital contractures and early pyramidal and extrapyramidal symptoms ⁸⁹ . |
| Consistency | | | |
| 10.1 | NA | NA | Confirmation. ZIKV-related adverse congenital outcomes in different regions (South America, Central America, and the Pacific region). The proportion of cases varies over geographic regions/time. |
| 10.2 | NA | NA | Confirmation. ZIKV exposure and adverse congenital outcome in different populations (people living in ZIKV endemic areas and travellers). |
| 10.3 | NA | NA | No publication with evidence of consistency across lineages due to circulation of single strain. |
| 10.4 | NA | NA | Confirmation. ZIKV exposure and adverse congenital outcomes found in different study types. |

from El Salvador that reported Chikungunya virus in 169 newborns of women with symptomatic infection; a minority had CNS infection, but microcephaly was not reported⁸⁸. For most analogous pathogens, infections earlier in the pregnancy have a higher risk of adverse outcomes⁸⁷.

Specificity. We included one study⁸⁹, suggesting an expansion of evidence of a distinct congenital Zika syndrome (CZS)⁸⁹. In a review of 34 published reports, the authors suggest five congenital abnormalities that, in conjunction, comprise a pattern that is unique to ZIKV: severe microcephaly with overlapping cranial structures, subcortical location of brain calcifications, macular scarring and retinal mottling, congenital contractures and early pyramidal and extrapyramidal symptoms⁸⁹.

Consistency. The studies included in this version of the review confirm the pattern of consistency observed in the baseline review. ZIKV infection in association with adverse congenital outcomes were reported in a range of study designs from different regions (WHO situation report 05.01.2017), although the proportion of affected infants varies over geographic region and time. ZIKV exposure resulted in adverse congenital outcome in people living in ZIKV endemic areas^{12–19,21–34,40–42,44,45,77,90,91} and in female travellers who returned to non-endemic countries^{34–39,92,93}. Direct evidence from epidemiological studies comparing different lineages is lacking due to circulation of a single strain.

Conclusion. The evidence added in update 1 of the review confirms the conclusion of a causal association between ZIKV and adverse congenital outcomes. New findings expand the evidence base in the dimensions of biological plausibility, strength of association, animal experiments and specificity. *In vitro* and *in vivo* studies elucidate pathways on how these outcomes likely occur. Conclusive evidence on the strength of association is lacking. Studies provide crude overall measures of association, not taking into account potential co-factors.

GBS/ITP

In the search period for update 1 of the review, an additional 154 cases of ZIKV-related GBS⁹⁵ and 11 ZIKV-related cases of ITP^{3–6} were described in 18 studies. Table 3 summarises the evidence for specific questions in each of 10 causality dimensions (detailed overview in Supplementary Table 3).

Temporality. We found an additional 17 publications that confirmed that ZIKV infection preceded the GBS or ITP at an individual level^{3,5,6,95–108} or at a population level^{103,109–111}. ZIKV infections seems to be followed by GBS on average between 5 and 10 days. In one case series from Colombia¹⁰³, the authors distinguished between rapid onset of GBS symptoms after ZIKV symptoms (para-infectious) and post-infectious onset, with an asymptomatic period after ZIKV symptoms before the start of GBS symptoms.

Table 3. Summary of the evidence on the relation between ZIKV infection and adverse autoimmune outcomes. Evidence is displayed for each dimension of the causality framework and for each question. Zika virus (ZIKV); Dengue virus (DENV); Guillain-Barré syndrome (GBS); immune-mediated idiopathic thrombocytopaenia purpura (ITP). NA, not applicable; evidence about analogous conditions was not searched systematically; the dimension of consistency used information in items included for all other causality dimensions. the baseline review (BR), Update 1 (U1).

| Question | BR, N | U1, N | Summary |
|---------------------------|-------|-------|---|
| Temporality | | | |
| 1.1a | 9 | 17 | Expansion of the evidence. Additional case reports and case series were identified that confirmed that ZIKV infection preceded adverse autoimmune outcomes ^{3,5,6,95-102,103-108} . |
| 1.1b | 9 | 4 | Expansion of the evidence that on the population level ZIKV precedes GBS or ITP ^{103,109-111} . |
| 1.2 | 7 | 14 | Expansion of evidence that the interval between exposure to ZIKV and occurrence of symptoms is typical for para- or post-infectious autoimmune-mediated disorders ^{5,6,95-102,103-106,112} . |
| Biological plausibility | | | |
| 2.1 | 3 | 0 | No additional evidence was identified that ZIKV epitopes mimic host antigens (molecular mimicry). |
| 2.2 | 1 | 0 | No additional evidence was identified that ZIKV infection leads to an increased in detectable autoreactive immune cells or autoreactive antibodies. |
| 2.3 | 0 | 0 | There is no evidence on other biologically plausible mechanisms of ZIKV infection leading to GBS/ITP. |
| Strength of association | | | |
| 3.1 | 1 | 0 | No additional evidence was identified on the association between Zika infection and GBS/ITP at the individual level. |
| 3.2 | 2 | 4 | Expansion of evidence. GBS incidence increased in several regions, during the same time ZIKV was circulating ^{103,109-111} . |
| Exclusion of alternatives | | | |
| 4.1 | 7 | 9 | Confirmation of the evidence where other infections were assessed. However, often previous DENV infection was reported, and not excluded ^{4-6,95,98,101,103,104,111} . |
| 4.2 | 0 | 1 | Expansion on the evidence where vaccines were excluded ⁵ . |
| 4.3 | 0 | 5 | Expansion on the evidence where other systemic illnesses were excluded ^{4-6,95,99,112} . |
| 4.4 | 0 | 2 | Expansion on the evidence where medication, drugs or other chemicals was excluded ^{99,112} . |
| Cessation | | | |
| 5.1 | 0 | 0 | No relevant studies identified that intentional removal or prevention of ZIKV infection in individuals leads to a reduction in cases with GBS/ITP. |
| 5.2 | 0 | 0 | No relevant studies identified that intentional removal or prevention of ZIKV infection at population level leads to a reduction in cases with GBS/ITP. |
| 5.3 | 6 | 2 | Expansion. Additionally, in Venezuela and the Dominican Republic, it was shown that GBS cases decreased with a decrease in reported ZIKV cases ^{103,111} . |
| Dose-response | | | |
| 6.1 | 0 | 0 | No relevant studies identified that the risk and the clinical severity of GBS/ITP are associated with viral titres. |
| Animal experiments | | | |
| 7.1 | 0 | 0 | No relevant studies identified where the inoculation of animals with ZIKV leads to an autoimmune reaction resulting in peripheral neuropathy or thrombocytopenia. |
| 7.2 | 0 | 0 | No relevant studies identified that other animal experiments support the association of ZIKV infection and GBS/ITP. |
| Analogy | | | |
| 8.1 | NA | NA | No additional studies identified that other flaviviruses or arboviruses cause GBS/ITP. |
| 8.2 | NA | NA | No additional studies identified that other pathogens cause GBS/ITP. |
| 8.3 | NA | NA | No additional studies identified that explain which pathogen or host factors facilitate the development of GBS/ITP. |
| Specificity | | | |
| 9.1 | 0 | 0 | No relevant studies identified that pathological findings in cases with GBS/ITP are specific for ZIKV infection. |

| Question | v1, N | v2, N | Summary |
|-------------|-------|-------|---|
| Consistency | | | |
| 10.1 | NA | NA | Confirmation that the association between ZIKV cases and cases with GBS is consistently found across different geographical regions. |
| 10.2 | NA | NA | Confirmation that the association between ZIKV cases and cases with GBS is consistently found across different populations/subpopulations. |
| 10.3 | NA | NA | No additional studies identified that the association between ZIKV cases and cases with GBS/ITP is consistently found across different ZIKV lineages/strains. |
| 10.4 | NA | NA | Confirmation that the association between ZIKV cases and cases with GBS is consistently found across different study designs. |

Biological plausibility. We did not find any publications about the biological plausibility of ZIKV as a cause of GBS or ITP.

Strength of association. We did not find any comparative observational studies during the search period for update 1. Several surveillance studies confirmed an increase in notified GBS cases during ZIKV outbreaks at the population level¹¹¹. Rate ratios were significantly higher for Brazil, Colombia, the Dominican Republic, El Salvador, Honduras, Suriname and Venezuela when comparing pre-ZIKV GBS incidence and the incidence during the outbreak¹¹¹; this ratio ranged from 2.0 (95% CI: 1.6-2.6) to 9.8 (95% CI: 7.6-12.5).

Exclusion of alternatives. We included 11 publications^{4-6,95,98,99,101,103,104,111,112} that expanded the list of alternative causes for autoimmune disease that were excluded, such as infections, vaccines, other system illnesses and medication, drugs or other chemicals. Many GBS cases in these publications had serological evidence of previous exposure to DENV, as seen in the baseline review. It remains unclear how large the potential role of co-factors such as antibody dependent enhancement are.

Cessation. We did not identify any publications with evidence about the effect of intentional removal/elimination/prevention of ZIKV on either GBS or ITP. An additional publication confirmed evidence that the natural removal of ZIKV resulted in a decrease in GBS cases in Brazil, Colombia, Dominican Republic, El Salvador, Honduras, Suriname and Venezuela^{104,111}.

Dose-response. We did not identify any publications about this dimension for either GBS or ITP.

Animal experiments. No additional evidence from animal experiments was identified that support the association between ZIKV infection and GBS/ITP development.

Analogy. As for the baseline review, evidence for this dimension was not reviewed systematically because our search strategy did not include terms for other infections or conditions. We did not identify any new publications addressing this dimension for either GBS or ITP.

Specificity. We did not identify any new publications addressing this dimension for either GBS or ITP.

Consistency. Studies included in update 1 confirmed the consistency of the evidence for 3 of 4 questions about the association between ZIKV and GBS. By geographical region, ZIKV transmission has been associated with the occurrence of GBS in 2 of 4 regions; increased GBS incidence has been reported in the WHO regions of the Americas and the Western Pacific region, but not in the African or Southeast Asian region, despite recent ZIKV circulation¹¹³. By study design, the association between ZIKV infection and GBS has been found at individual and population level and with different study designs. By population, ZIKV infection has been linked to GBS in ZIKV endemic regions^{4-6,95,96,98-101,103-105,109,111,114} and travellers from non-affected countries who were exposed in these endemic regions^{3,97,102,106,112}. There was insufficient evidence to examine the consistency of evidence about ZIKV and ITP.

Conclusion. The body of evidence has grown during the search period for update 1 but only for dimensions that were already populated in the original publication for GBS. There is still a limited understanding of the biological pathways that potentially cause the occurrence of autoimmune disease following ZIKV infection. Additionally, prospective comparative epidemiological studies are still lacking. It remains unclear how co-factors such as age and previous exposure to flaviviruses influences the risk of developing GBS. The evidence supports a temporal association between ZIKV and ITP but there is an absence of evidence for other dimensions of causality.

Search results from January 19, 2017 to January 05, 2018

Automated search and deduplication processes identified 2410 publications about any aspect of ZIKV infection. The next update of this review will address causality dimensions in the realm of epidemiological studies; strength of association, dose-response relationship, specificity and consistency.

Discussion

Statement of principal findings. This systematic review confirms evidence of a causal association between ZIKV and adverse congenital outcomes and between ZIKV and GBS, although

evidence about biological plausibility is still lacking. We assessed evidence about an association between ZIKV and ITP but found that this only addressed the dimension of temporality. The review is transitioning from classic systematic review methods to those of a living systematic review.

Strengths and limitations of the study. The strengths of this study are the systematic approach to the identification, selection and extraction of data following a causality framework that provides a structure for the consideration of heterogeneous sources of evidence and a large set of review questions. Automation of the review output allows rapid updating of tables of results. We have also developed methods to automate search and deduplication of search results to make the transition to a living systematic review that will allow continual updating of results. The main limitation of the classic systematic review of such a complex topic is the high workload and time required to maintain it. Another limitation, resulting from the large number of review questions, is the time taken to resolve inter-reviewer differences in interpretation of eligibility criteria. This could have resulted in subjectivity over decisions about inclusion in the review. Although a second reviewer checked all extractions, changes in the review team could introduce inconsistency. As in the baseline review, we used case definitions as authors described them in individual publications. This potential source of information bias is likely to decrease over time as standardised case definitions and protocols are adopted¹¹⁵. As in the previous version, we did not systematically apply quality assessment tools to individual studies. Because much of the technical infrastructure was built as the evidence emerged, output was delayed. As much of the LSR methodology was novel, it took time to find a balance between speed and efficiency.

Strengths and weaknesses in relation to other publications. Our systematic review differs from most standard reviews because of the number of questions within the dimensions of the causality framework and the number of outcomes. Other recent examples of living systematic reviews only distinguish between two study types (RCT and non-RCT)¹¹⁶ and are guided by only a small set of review questions^{117,118}. Our review conclusion, confirming evidence for a causal association between ZIKV and GBS differs from that of a review¹¹⁹ of the findings of four case reports^{104,120–122} and one case-control study¹²³. The authors found insufficient evidence to confirm the presence of an acute motor axonal neuropathy variant of GBS. They did not, however, suggest an alternative explanation for the increase in incidence of GBS in the countries that experienced ZIKV outbreaks. The two versions of our review included 64 publications about ZIKV and GBS across ten dimensions of causality.

Meaning of the study: possible mechanisms and implications for basic researchers, clinicians or policymakers. The conclusions on the causal relation between ZIKV and adverse congenital outcomes and ZIKV and GBS did not change with this update. We found insufficient evidence about the association between ZIKV and ITP to state with certainty that there

is a causal association. The total volume of evidence about the association between ZIKV and GBS is less than for the association with adverse congenital outcomes. There is, in particular a lack of published research to elucidate biological mechanisms for direct neuronal or autoimmune damage in GBS¹²⁴. The descriptive data about the numbers and types of different studies over time illustrates how evidence about a new, or re-emerging, infection emerges over time. The evidence from many regions that were affected by the ZIKV outbreak remains limited to anecdotal evidence of adverse outcomes, in the form of case reports or case series. The slowing of ZIKV transmission in 2017 means that fewer people are being affected by ZIKV and its complications and fewer people are being enrolled into prospective studies. Further progress in epidemiological research will rely more heavily on research consortia who are contributing to joint analyses of data from existing studies.

Unanswered questions and future research. As the volume and complexity of the evidence in different causality dimensions accumulates, the need for expert input and interpretation of the findings of this systematic review increases. The focus of research on ZIKV and causal associations with different types of adverse outcomes is also changing. For congenital abnormalities resulting from ZIKV vertical transmission, epidemiological research should examine CZS in comparative studies, quantify the strength of association with ZIKV, clarify associations with gestational age, symptomatology and viral load and further investigate potential co-factors such as previous dengue infection and flavivirus vaccination. WHO standardised study protocols provide suggestions for exclusion of alternative explanations and exploration of co-factors ([Harmonization of ZIKV Research Protocols](#)). For GBS, epidemiological studies are needed to quantify the association with ZIKV more precisely, but also to determine whether there are distinct phenotypes resulting from autoimmune mechanisms or direct neuronal involvement. For ITP, additional evidence across all causality dimensions is needed.

Planned updates of a living systematic review. Living systematic review methodology and techniques will continue to develop. Since a chain is only as strong as its weakest link, any processing step has the potential to slow down a living systematic review. Clearly defined protocols that define update frequencies and throughput speed of different actors in the publishing process are vital. The next update of the systematic reviews will use living systematic review methods to assess the evidence for 2017 and early 2018 (update 2, [Figure 2](#)). The review will, for the first time, separate evidence from epidemiological study designs from *in vitro* and *in vivo* laboratory studies. We will narrow down the inclusion criteria based on study type. Epidemiological evidence will address the causality dimensions ‘strength of association’, ‘dose-response’, ‘specificity’ and ‘consistency’. Several co-factors might play a role in the strength of association. Thus, we will continue to collect information on previous dengue virus infection, yellow fever vaccination status, socioeconomic status, gestational age and others factors

that might play a role in the severity of the outcome. We will amend the protocol with a more focused search strategy and inclusion criteria ([Supplementary File 3](#)).

Systematic reviews of questions addressed by laboratory studies are less frequent than those addressing epidemiological research questions. There is still need to update understanding of the causality dimensions ‘biological plausibility’ and ‘animal experiments’, particularly to increase our understanding of biological pathways for ZIKV effects on the peripheral nervous system and the immune system. We encourage and welcome collaboration from scientists with expertise in these fields to update systematic reviews for these causality dimensions.

Conclusion. This systematic review confirms previous conclusions that ZIKV is a cause of congenital abnormalities, including microcephaly and is a trigger of GBS. Evidence suggests an association with idiopathic thrombocytopaenia purpura but is not conclusive. The transition to living systematic review techniques and methodology provides a proof of concept for the use of these methods to synthesise evidence about an emerging pathogen such as ZIKV, ultimately leading to integration in the whole public health information cycle¹²⁵. With the infrastructure for living systematic review methods and open source access to the software

and outputs, we aim to enhance outbreak preparedness and the study of emerging and re-emerging pathogens.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Competing interests

No competing interests were disclosed.

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Supplementary material

Supplementary Table 1 – Bradford Hill’s “viewpoints” of causation.

[Click here to access the data.](#)

Supplementary Table 2 – Evidence table adverse congenital outcomes update 1.

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Supplementary Table 3 – Evidence table GBS/ITP update 1.

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Supplementary File 1 – PRISMA Checklist.

[Click here to access the data.](#)

Supplementary File 2 – LSR automation methodology.

[Click here to access the data.](#)

Supplementary File 3 – Search strategy update 2.

[Click here to access the data.](#)

References

1. Broutet N, Krauer F, Riesen M, *et al.*: **Zika Virus as a Cause of Neurologic Disorders.** *N Engl J Med.* 2016; **374**(16): 1506–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
2. Rasmussen SA, Jamieson DJ, Honein MA, *et al.*: **Zika Virus and Birth Defects—Reviewing the Evidence for Causality.** *N Engl J Med.* 2016; **374**(20): 1981–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
3. de Laval F, Matheus S, Maquart M, *et al.*: **Prospective Zika virus disease cohort: systematic screening.** *Lancet.* 2016; **388**(10047): 868.
[PubMed Abstract](#) | [Publisher Full Text](#)
4. Chraïbi S, Najioullah F, Bourdin C, *et al.*: **Two cases of thrombocytopenic purpura at onset of Zika virus infection.** *J Clin Virol.* 2016; **83**(34): 61–2.
[PubMed Abstract](#) | [Publisher Full Text](#)

5. Boyer Chamard T, Schepers K, Breurec S, *et al.*: **Severe Thrombocytopenia after Zika Virus Infection, Guadeloupe, 2016.** *Emerg Infect Dis.* 2017; 23(4): 696–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
6. Zea-Vera AF, Parra B: **Zika virus (ZIKV) infection related with immune thrombocytopenic purpura (ITP) exacerbation and antinuclear antibody positivity.** *Lupus.* 2017; 26(8): 890–2.
[PubMed Abstract](#) | [Publisher Full Text](#)
7. Krauer F, Riesen M, Reveiz L, *et al.*: **Zika Virus Infection as a Cause of Congenital Brain Abnormalities and Guillain-Barré Syndrome: Systematic Review.** *PLoS Med.* 2017; 14(1): e1002203.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
8. Hill AB: **The Environment and Disease: Association or Causation?** *Proc R Soc Med.* 1965; 58(5): 295–300.
[PubMed Abstract](#) | [Free Full Text](#)
9. Elliott JH, Turner T, Clavisi O, *et al.*: **Living systematic reviews: an emerging opportunity to narrow the evidence-practice gap.** *PLoS Med.* 2014; 11(2): e1001603.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
10. Elliott JH, Synnot A, Turner T, *et al.*: **Living systematic review: 1. Introduction-the why, what, when, and how.** *J Clin Epidemiol.* 2017; 91: 23–30.
[PubMed Abstract](#) | [Publisher Full Text](#)
11. Moher D, Liberati A, Tetzlaff J, *et al.*: **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.** *PLoS Med.* 2009; 6(7): e1000097.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
12. Leal MC, Muniz LF, Caldas Neto SD, *et al.*: **Sensorineural hearing loss in a case of congenital Zika virus.** *Braz J Otorhinolaryngol.* 2016; pii: S1808-8694(16)30127-6.
[PubMed Abstract](#) | [Publisher Full Text](#)
13. França GV, Schuler-Faccini L, Oliveira WK, *et al.*: **Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation.** *Lancet.* 2016; 388(10047): 891–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
14. Martines RB, Bhatnagar J, de Oliveira Ramos AM, *et al.*: **Pathology of congenital Zika syndrome in Brazil: a case series.** *Lancet.* 2016; 388(10047): 898–904.
[PubMed Abstract](#) | [Publisher Full Text](#)
15. Carvalho FH, Cordeiro KM, Peixoto AB, *et al.*: **Associated ultrasonographic findings in fetuses with microcephaly because of suspected Zika virus (ZIKV) infection during pregnancy.** *Prenat Diagn.* 2016; 36(9): 882–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
16. Bhadelia N: **Prospective cohort study of pregnant Brazilian women elucidates link between Zika virus infection and fetal abnormalities.** *Evid Based Med.* 2016; 21(5): 193.
[PubMed Abstract](#) | [Publisher Full Text](#)
17. van der Linden V, Filho EL, Lins OG, *et al.*: **Congenital Zika syndrome with arthrogryposis: retrospective case series study.** *BMJ.* 2016; 354(8): i3899.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
18. Leal MC, Muniz LF, Ferreira TS, *et al.*: **Hearing Loss in Infants with Microcephaly and Evidence of Congenital Zika Virus Infection - Brazil, November 2015-May 2016.** *MMWR Morb Mortal Wkly Rep.* 2016; 65(34): 917–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
19. Soares de Souza A, Moraes Dias C, Braga FD, *et al.*: **Fetal Infection by Zika Virus in the Third Trimester: Report of 2 Cases.** *Clin Infect Dis.* 2016; 63(12): 1622–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
20. De Paiva Cavalcante T, De Campos JGG, De Freire MRM, *et al.*: **Congenital neural tube defects evaluation in newborns with prenatal Zika virus infection.** *Child's Nervous System.* 2016; 32(5): 933.
[Publisher Full Text](#)
21. Thalia Velho Barreto A, Laura CR, Ricardo AX, *et al.*: **Microcephaly and Zika infection: Preliminary Report of a Case-Control Study.** *Lancet.* 2016; 16(12): 1356–63.
22. de Araújo TVB, Rodrigues LC, de Alencar Ximenes RA, *et al.*: **Association between Zika virus infection and microcephaly in Brazil, January to May, 2016: preliminary report of a case-control study.** *Lancet Infect Dis.* 2016; 16(12): 1356–63.
[PubMed Abstract](#) | [Publisher Full Text](#)
23. Melo AS, Aguiar RS, Amorim MM, *et al.*: **Congenital Zika Virus Infection: Beyond Neonatal Microcephaly.** *JAMA Neurol.* 2016; 73(12): 1407–16.
[PubMed Abstract](#) | [Publisher Full Text](#)
24. van der Linden V, Pessoa A, Dobyns W, *et al.*: **Description of 13 Infants Born During October 2015-January 2016 With Congenital Zika Virus Infection Without Microcephaly at Birth - Brazil.** *MMWR Morb Mortal Wkly Rep.* 2016; 65(47): 1343–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
25. João EC, Gouveia MI, Teixeira ML, *et al.*: **Zika Virus Infection Associated With Congenital Birth Defects in a HIV-infected Pregnant Woman.** *Pediatr Infect Dis J.* 2017; 36(5): 500–1.
[PubMed Abstract](#) | [Publisher Full Text](#)
26. Moura da Silva AA, Ganz JS, Sousa PD, *et al.*: **Early Growth and Neurologic Outcomes of Infants with Probable Congenital Zika Virus Syndrome.** *Emerg Infect Dis.* 2016; 22(11): 1953–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
27. de Paula Freitas B, Ko AI, Khouri R, *et al.*: **Glaucoma and Congenital Zika Syndrome.** *Ophthalmology.* 2017; 124(3): 407–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
28. Campos AG, Lira RP, Arantes TE: **Optical coherence tomography of macular atrophy associated with microcephaly and presumed intrauterine Zika virus infection.** *Arq Bras Oftalmol.* 2016; 79(6): 400–1.
[PubMed Abstract](#) | [Publisher Full Text](#)
29. Vargas A, Saad E, Dimech GS, *et al.*: **Characteristics of the first cases of microcephaly possibly related to Zika virus reported in the Metropolitan Region of Recife, Pernambuco State, Brazil.** *Epidemiol Serv Saude.* 2016; 25(4): 691–700.
[PubMed Abstract](#) | [Publisher Full Text](#)
30. Werner H, Fazecas T, Guedes B, *et al.*: **Intrauterine Zika virus infection and microcephaly: correlation of perinatal imaging and three-dimensional virtual physical models.** *Ultrasound Obstet Gynecol.* 2016; 47(5): 657–60.
[PubMed Abstract](#) | [Publisher Full Text](#)
31. Brasil P, Pereira JP Jr, Moreira ME, *et al.*: **Zika Virus Infection in Pregnant Women in Rio de Janeiro.** *N Engl J Med.* 2016; 375(24): 2321–34.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
32. Honein MA, Dawson AL, Petersen EE, *et al.*: **Birth Defects Among Fetuses and Infants of US Women With Evidence of Possible Zika Virus Infection During Pregnancy.** *JAMA.* 2017; 317(1): 59–68.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. Bhatnagar J, Rabeneck DB, Martines RB, *et al.*: **Zika Virus RNA Replication and Persistence in Brain and Placental Tissue.** *Emerg Infect Dis.* 2017; 23(3): 405–14.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
34. Adams L, Bello-Pagan M, Lozier M, *et al.*: **Update: Ongoing Zika Virus Transmission - Puerto Rico, November 1, 2015-July 7, 2016.** *MMWR Morb Mortal Wkly Rep.* 2016; 65(30): 774–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
35. Meaney-Delman D, Oduyebo T, Polen KN, *et al.*: **Prolonged Detection of Zika Virus RNA in Pregnant Women.** *Obstet Gynecol.* 2016; 128(4): 724–30.
[PubMed Abstract](#) | [Publisher Full Text](#)
36. van der Eijk AA, van Genderen PJ, Verdijk RM, *et al.*: **Miscarriage Associated with Zika Virus Infection.** *N Engl J Med.* 2016; 375(10): 1002–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Suy A, Sulleiro E, Rodó C, *et al.*: **Prolonged Zika Virus Viremia during Pregnancy.** *N Engl J Med.* 2016; 375(26): 2611–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
38. Ventura CV, Fernandez MP, Gonzalez IA, *et al.*: **First Travel-Associated Congenital Zika Syndrome in the US: Ocular and Neurological Findings in the Absence of Microcephaly.** *Ophthalmic Surg Lasers Imaging Retina.* 2016; 47(10): 952–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
39. Herrera K, Bernasko J, Garry D, *et al.*: **Vertical transmission of Zika virus (ZIKV) in early pregnancy: two cases, two different courses.** *Case Reports in Perinatal Medicine.* 2016; 5(2): 131–3.
[Publisher Full Text](#)
40. Pomar L, Malingier G, Benoist G, *et al.*: **Association between Zika virus and fetopathy: a prospective cohort study in French Guiana.** *Ultrasound Obstet Gynecol.* 2017; 49(6): 729–36.
[PubMed Abstract](#) | [Publisher Full Text](#)
41. Kumar M, Ching L, Astern J, *et al.*: **Prevalence of Antibodies to Zika Virus in Mothers from Hawaii Who Delivered Babies with and without Microcephaly between 2009–2012.** *PLoS Negl Trop Dis.* 2016; 10(12): e0005262.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
42. Schaub B, Monthieux A, Najjoulah F, *et al.*: **Persistent maternal Zika viremia: a marker of fetal infection.** *Ultrasound Obstet Gynecol.* 2017; 49(5): 658–60.
[PubMed Abstract](#) | [Publisher Full Text](#)
43. Villamil-Gómez WE, Rodríguez-Morales AJ, Uribe-García AM, *et al.*: **Zika, dengue, and chikungunya co-infection in a pregnant woman from Colombia.** *Int J Infect Dis.* 2016; 51: 135–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
44. Sanin-Blair JCA, Gutierrez-Marín J, Campo-Campo M, *et al.*: **Fetal ultrasound findings in Zika infection. Preliminary report in a Colombian selected population.** *Journal of Maternal-Fetal and Neonatal Medicine.* 2016; 29(2): 163–4.
45. Cuevas EL, Tong VT, Rozo N, *et al.*: **Preliminary Report of Microcephaly Potentially Associated with Zika Virus Infection During Pregnancy - Colombia, January–November 2016.** *MMWR Morb Mortal Wkly Rep.* 2016; 65(49): 1409–13.
[PubMed Abstract](#) | [Publisher Full Text](#)
46. Magalhães-Barbosa MC, Prata-Barbosa A, Robaina JR, *et al.*: **Trends of the microcephaly and Zika virus outbreak in Brazil, January–July 2016.** *Travel Med Infect Dis.* 2016; 14(5): 458–63.
[PubMed Abstract](#) | [Publisher Full Text](#)
47. Tabata T, Pettit M, Puerta-Guardo H, *et al.*: **Zika Virus Targets Different Primary Human Placental Cells, Suggesting Two Routes for Vertical Transmission.** *Cell Host Microbe.* 2016; 20(2): 155–66.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
48. Onorati M, Li Z, Liu F, *et al.*: **Zika Virus Disrupts Phospho-TBK1 Localization and Mitosis in Human Neuroepithelial Stem Cells and Radial Glia.** *Cell Rep.* 2016; 16(10): 2576–92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
49. Sironi M, Forni D, Clerici M, *et al.*: **Nonstructural Proteins Are Preferential**

- Positive Selection Targets in Zika Virus and Related Flaviviruses.** *PLoS Negl Trop Dis.* 2016; 10(9): e0004978.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
50. Retallack H, Di Lullo E, Arias C, *et al.*: Zika Virus in the Human Placenta and Developing Brain: Cell Tropism and Drug Inhibition. *bioRxiv.* 2016; 058883.
[Publisher Full Text](#)
 51. Retallack H, Di Lullo E, Arias C, *et al.*: Zika virus cell tropism in the developing human brain and inhibition by azithromycin. *Proc Natl Acad Sci U S A.* 2016; 113(50): 14408–13.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 52. Liu S, DeLalio LJ, Isakson BE, *et al.*: AXL-Mediated Productive Infection of Human Endothelial Cells by Zika Virus. *Circ Res.* 2016; 119(11): 1183–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 53. Tssetsarkin KA, Kenney H, Chen R, *et al.*: A Full-Length Infectious cDNA Clone of Zika Virus from the 2015 Epidemic in Brazil as a Genetic Platform for Studies of Virus-Host Interactions and Vaccine Development. *mBio.* 2016; 7(4): e01114–16.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 54. Jurado KA, Simoni MK, Tang Z, *et al.*: Zika virus productively infects primary human placenta-specific macrophages. *JCI Insight.* 2016; 1(13): pii: e88461.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 55. El Costa H, Gouilly J, Mansuy JM, *et al.*: ZIKA virus reveals broad tissue and cell tropism during the first trimester of pregnancy. *Sci Rep.* 2016; 6: 35296.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 56. Hanners NW, Eitson JL, Usui N, *et al.*: Western Zika Virus in Human Fetal Neural Progenitors Persists Long Term with Partial Cytopathic and Limited Immunogenic Effects. *Cell Rep.* 2016; 15(11): 2315–22.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 57. Liang Q, Luo Z, Zeng J, *et al.*: Zika Virus NS4A and NS4B Proteins Deregulate Akt-mTOR Signaling in Human Fetal Neural Stem Cells to Inhibit Neurogenesis and Induce Autophagy. *Cell Stem Cell.* 2016; 19(5): 663–71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 58. Garcez PP, Nascimento JM, Mota de Vasconcelos J, *et al.*: Combined proteome and transcriptome analyses reveal that Zika virus circulating in Brazil alters cell cycle and neurogenic programmes in human neurospheres. *PeerJ Preprints.* 2016; 4: e2033v1.
[Publisher Full Text](#)
 59. Bayless NL, Greenberg RS, Swigut T, *et al.*: Zika Virus Infection Induces Cranial Neural Crest Cells to Produce Cytokines at Levels Detrimental for Neurogenesis. *Cell Host Microbe.* 2016; 20(4): 423–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 60. Barreras P, Pamies D, Kumar A, *et al.*: 2016 Annual Meetings. *Ann Neurol.* 2016; 80(s20): S1–S432.
[PubMed Abstract](#) | [Publisher Full Text](#)
 61. Hughes BW, Addanki KC, Sriskanda AN, *et al.*: Infectivity of Immature Neurons to Zika Virus: A Link to Congenital Zika Syndrome. *EBioMedicine.* 2016; 10(10038): 65–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 62. Kumar A, Singh HN, Pareek V, *et al.*: A Possible Mechanism of Zika Virus Associated Microcephaly: Imperative Role of Retinoic Acid Response Element (RARE) Consensus Sequence Repeats in the Viral Genome. *Front Hum Neurosci.* 2016; 10: 403.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 63. Chan JF, Yip CC, Tsang JO, *et al.*: Differential cell line susceptibility to the emerging Zika virus: implications for disease pathogenesis, non-vector-borne human transmission and animal reservoirs. *Emerg Microbes Infect.* 2016; 5: e93.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 64. Xu M, Lee EM, Wen Z, *et al.*: Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen. *Nat Med.* 2016; 22(10): 1101–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 65. Zhang F, Hammack C, Ogden SC, *et al.*: Molecular signatures associated with ZIKV exposure in human cortical neural progenitors. *Nucleic Acids Res.* 2016; 44(18): 8610–20.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 66. Nogueira FCS, Velasquez E, Melo ASO, *et al.*: Zika virus may not be alone: proteomics associates a bovine-like viral diarrhea virus to microcephaly. *bioRxiv.* 2016; 062596.
[Publisher Full Text](#)
 67. Wang Z, Ma'ayan A: An open RNA-Seq data analysis pipeline tutorial with an example of reprocessing data from a recent Zika virus study [version 1; referees: 3 approved]. *F1000Res.* 2016; 5(1574): 1574.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 68. Weisblum Y, Oiknine-Djian E, Vorontsov OM, *et al.*: Zika Virus Infects Early- and Midgestation Human Maternal Decidual Tissues, Inducing Distinct Innate Tissue Responses in the Maternal-Fetal Interface. *J Virol.* 2017; 91(4): pii: e01905-16.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 69. Li Y, Muffat J, Omer A, *et al.*: Induction of Expansion and Folding in Human Cerebral Organoids. *Cell Stem Cell.* 2017; 20(3): 385–96 e3.
[PubMed Abstract](#) | [Publisher Full Text](#)
 70. Souza BS, Sampaio GL, Pereira CS, *et al.*: Zika virus infection induces mitosis abnormalities and apoptotic cell death of human neural progenitor cells. *Sci Rep.* 2016; 6: 39775.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 71. Aldo P, You Y, Szigeti K, *et al.*: HSV-2 enhances ZIKV infection of the placenta and induces apoptosis in first-trimester trophoblast cells. *Am J Reprod Immunol.* 2016; 76(5): 348–57.
[PubMed Abstract](#) | [Publisher Full Text](#)
 72. Lucchese G, Kanduc D: Minimal immune determinants connect Zika virus, human Cytomegalovirus, and *Toxoplasma gondii* to microcephaly-related human proteins. *Am J Reprod Immunol.* 2017; 77(2): e12608.
[PubMed Abstract](#) | [Publisher Full Text](#)
 73. Simonin Y, Loustalot F, Desmetz C, *et al.*: Zika Virus Strains Potentially Display Different Infectious Profiles in Human Neural Cells. *EBioMedicine.* 2016; 12: 161–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 74. Kodani AT, Reiter JF, Knopp K, *et al.*: Zika infection disrupts centriole biogenesis. *Mol Biol Cell.* 2016; 27(25): 4182–3.
[Publisher Full Text](#)
 75. Veilleux C, Eugenin E: Characterization of Zika virus infection in Human Astrocytes. *J Neurovirol.* 2016; 22: S78–S9.
[Publisher Full Text](#)
 76. Yaffe Y, Dellibovi-Ragheb TA, Chen Y, *et al.*: Board Number: B456 The role of centrosomes in the pathogenesis of Zika virus (ZIKV)-related microcephaly. *Mol Biol Cell.* 2016; 27(25): 4919.
[Publisher Full Text](#)
 77. Oliveira DB, Almeida FJ, Durigon EL, *et al.*: Prolonged Shedding of Zika Virus Associated with Congenital Infection. *N Engl J Med.* 2016; 375(12): 1202–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
 78. Adams Waldorf KM, Stencel-Baerenwald JE, Kapur RP, *et al.*: Fetal brain lesions after subcutaneous inoculation of Zika virus in a pregnant nonhuman primate. *Nat Med.* 2016; 22(11): 1256–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 79. Manangeeswaran M, Ireland DD, Verthelyi D: Zika (PRVABC59) Infection Is Associated with T cell Infiltration and Neurodegeneration in CNS of Immunocompetent Neonatal C57BL/6 Mice. *PLoS Pathog.* 2016; 12(11): e1006004.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 80. Goodfellow FT, Tesla B, Simchick G, *et al.*: Zika Virus Induced Mortality and Microcephaly in Chicken Embryos. *Stem Cells Dev.* 2016; 25(22): 1691–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 81. Shao Q, Herrlinger S, Yang SL, *et al.*: Zika virus infection disrupts neurovascular development and results in postnatal microcephaly with brain damage. *Development.* 2016; 143(22): 4127–36.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 82. Huang WC, Abraham R, Shim BS, *et al.*: Zika virus infection during the period of maximal brain growth causes microcephaly and corticospinal neuron apoptosis in wild type mice. *Sci Rep.* 2016; 6: 34793.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 83. Doobin DJ, Rosenfeld A, Carabalona A, *et al.*: Genetic and infectious causes of microcephaly caused by NDE1 mutations and Zika virus. *Molecular Biology of the Cell.* 2016; 27(25): 4129–30.
 84. Yockey LJ, Varela L, Rakib T, *et al.*: Vaginal Exposure to Zika Virus during Pregnancy Leads to Fetal Brain Infection. *Cell.* 2016; 166(5): 1247–56 e4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 85. Cugola FR, Fernandes IR, Russo FB, *et al.*: The Brazilian Zika virus strain causes birth defects in experimental models. *Nature.* 2016; 534(7606): 267–71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 86. Brault JB, Khou C, Basset J, *et al.*: Comparative Analysis Between Flaviviruses Reveals Specific Neural Stem Cell Tropism for Zika Virus in the Mouse Developing Neocortex. *EBioMedicine.* 2016; 10(2): 71–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 87. Panchaud A, Stojanov M, Ammerdorffer A, *et al.*: Emerging Role of Zika Virus in Adverse Fetal and Neonatal Outcomes. *Clin Microbiol Rev.* 2016; 29(3): 659–94.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 88. Torres JR, Falleiros-Arlant LH, Dueñas L, *et al.*: Congenital and perinatal complications of chikungunya fever: a Latin American experience. *Int J Infect Dis.* 2016; 51: 85–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 89. Moore CA, Staples JE, Dobyns WB, *et al.*: Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians. *JAMA Pediatr.* 2017; 171(3): 288–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 90. Soares de Oliveira-Szejnfeld P, Levine D, Melo AS, *et al.*: Congenital Brain Abnormalities and Zika Virus: What the Radiologist Can Expect to See Prenatally and Postnatally. *Radiology.* 2016; 281(1): 203–18.
[PubMed Abstract](#) | [Publisher Full Text](#)
 91. Sarno M, Aquino M, Pimentel K, *et al.*: Progressive lesions of central nervous system in microcephalic fetuses with suspected congenital Zika virus syndrome. *Ultrasound Obstet Gynecol.* 2017; 50(6): 717–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
 92. Štráfel P, Vizjak A, Mraz J, *et al.*: Zika Virus-Associated Microcephaly: A Thorough Description of Neuropathologic Findings in the Fetal Central Nervous System. *Arch Pathol Lab Med.* 2017; 141(1): 73–81.
[PubMed Abstract](#) | [Publisher Full Text](#)
 93. Vesnaver TV, Tul N, Mehrabi S, *et al.*: Zika virus associated microcephaly/microcephaly-fetal brain imaging in comparison with neuropathology. *BJOG.*

- 2017; **124**(3): 521–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
94. Acosta-Reyes J, Navarro E, Herrera MJ, *et al.*: **Severe Neurologic Disorders in 2 Fetuses with Zika Virus Infection, Colombia.** *Emerg Infect Dis.* 2017; **23**(6): 982–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 95. Zambrano H, Waggoner JJ, Almeida C, *et al.*: **Zika Virus and Chikungunya Virus Coinfections: A Series of Three Cases from a Single Center in Ecuador.** *Am J Trop Med Hyg.* 2016; **95**(4): 894–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 96. Dirlikov E, Major CG, Mayshack M, *et al.*: **Guillain-Barré Syndrome During Ongoing Zika Virus Transmission - Puerto Rico, January 1-July 31, 2016.** *MMWR Morb Mortal Wkly Rep.* 2016; **65**(34): 910–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
 97. Medina MT, England JD, Lorenzana I, *et al.*: **Zika virus associated with sensory polyneuropathy.** *J Neurol Sci.* 2016; **369**(30): 271–2.
[PubMed Abstract](#) | [Publisher Full Text](#)
 98. Langerak T, Yang H, Baptista M, *et al.*: **Zika Virus Infection and Guillain-Barré Syndrome in Three Patients from Suriname.** *Front Neurol.* 2016; **7**(11): 233.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 99. Arias A, Torres-Tobar L, Hernández G, *et al.*: **Guillain-Barré syndrome in patients with a recent history of Zika in Cúcuta, Colombia: A descriptive case series of 19 patients from December 2015 to March 2016.** *J Crit Care.* 2017; **37**: 19–23.
[PubMed Abstract](#) | [Publisher Full Text](#)
 100. Anaya JM, Rodríguez Y, Monsalve DM, *et al.*: **A comprehensive analysis and immunobiology of autoimmune neurological syndromes during the Zika virus outbreak in Cúcuta, Colombia.** *J Autoimmun.* 2017; **77**: 123–38.
[PubMed Abstract](#) | [Publisher Full Text](#)
 101. do Rosário MS, de Jesus PA, Vasilakis N, *et al.*: **Guillain-Barré Syndrome After Zika Virus Infection in Brazil.** *Am J Trop Med Hyg.* 2016; **95**(5): 1157–60.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 102. Fabrizius RG, Anderson K, Hendel-Paterson B, *et al.*: **Guillain-Barré Syndrome Associated with Zika Virus Infection in a Traveler Returning from Guyana.** *Am J Trop Med Hyg.* 2016; **95**(5): 1161–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 103. Parra B, Lizarazo J, Jiménez-Arango JA, *et al.*: **Guillain-Barré Syndrome Associated with Zika Virus Infection in Colombia.** *N Engl J Med.* 2016; **375**(16): 1513–23.
[PubMed Abstract](#) | [Publisher Full Text](#)
 104. Fontes CA, Dos Santos AA, Marchiori E: **Magnetic resonance imaging findings in Guillain-Barré syndrome caused by Zika virus infection.** *Neuroradiology.* 2016; **58**(8): 837–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 105. Langerak T, Yang H, Baptista M, *et al.*: **Zika Virus Infection and Guillain-Barré Syndrome in Three Patients from Suriname.** *Front Neurol.* 2016; **7**: 233.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 106. Skrove JL, Salhab J, Colella DM, *et al.*: **Zika virus: A rare case with presenting symptoms of gastroenteritis and transaminitis with subsequent progression to Guillain-Barré syndrome.** *Am J Gastroenterol.* 2016; **111**: S975–S6.
[Publisher Full Text](#)
 107. Septfons A, Leparc-Goffart I, Couturier E, *et al.*: **Travel-associated and autochthonous Zika virus infection in mainland France, 1 January to 15 July 2016.** *Euro Surveill.* 2016; **21**(32).
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 108. Walker WL, Lindsey NP, Lehman JA, *et al.*: **Zika Virus Disease Cases - 50 States and the District of Columbia, January 1-July 31, 2016.** *MMWR Morb Mortal Wkly Rep.* 2016; **65**(36): 983–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 109. Ferreira da Silva IR, Frontera JA, Moreira do Nascimento OJ: **News from the battlefield: Zika virus-associated Guillain-Barré syndrome in Brazil.** *Neurology.* 2016; **87**(15): e180–e1.
[PubMed Abstract](#) | [Publisher Full Text](#)
 110. Machado-Alba JE, Machado-Duque ME, Gaviria-Mendoza A, *et al.*: **Diagnosis of neurological disorders and the Zika virus epidemic in Colombia 2014 -2016.** *Int J Infect Dis.* 2016; **51**: 133–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
 111. Dos Santos T, Rodríguez A, Almiron M, *et al.*: **Zika Virus and the Guillain-Barré Syndrome - Case Series from Seven Countries.** *N Engl J Med.* 2016; **375**(16): 1598–601.
[PubMed Abstract](#) | [Publisher Full Text](#)
 112. Siu R, Bukhari W, Todd A, *et al.*: **Acute Zika infection with concurrent onset of Guillain-Barré Syndrome.** *Neurology.* 2016; **87**(15): 1623–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
 113. World Health Organization: **WHO | Zika situation report 05-01-2017.** 2017.
[Reference Source](#)
 114. Lee CT, Vora NM, Bajwa W, *et al.*: **Zika Virus Surveillance and Preparedness - New York City, 2015-2016.** *MMWR Morb Mortal Wkly Rep.* 2016; **65**(24): 629–35.
[PubMed Abstract](#) | [Publisher Full Text](#)
 115. Van Kerkhove MD, Reveiz L, Souza JP, *et al.*: **Harmonisation of Zika virus research protocols to address key public health concerns.** *Lancet Glob Health.* 2016; **4**(12): e911–e2.
[PubMed Abstract](#) | [Publisher Full Text](#)
 116. Wallace BC, Noel-Storr A, Marshall IJ, *et al.*: **Identifying reports of randomized controlled trials (RCTs) via a hybrid machine learning and crowdsourcing approach.** *J Am Med Inform Assoc.* 2017; **24**(6): 1165–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 117. Akl EA, Kahale LA, Hakoum MB, *et al.*: **Parenteral anticoagulation in ambulatory patients with cancer.** *Cochrane Database Syst Rev.* 2017; **9**: Cd006652.
[PubMed Abstract](#) | [Publisher Full Text](#)
 118. Spurling GK, Del Mar CB, Dooley L, *et al.*: **Delayed antibiotic prescriptions for respiratory infections.** *Cochrane Database Syst Rev.* 2017; **9**: Cd004417.
[PubMed Abstract](#) | [Publisher Full Text](#)
 119. Leis AA, Stokic DS: **Zika Virus and Guillain-Barre Syndrome: Is There Sufficient Evidence for Causality?** *Front Neurol.* 2016; **7**(1): 170.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 120. Oehler E, Watrin L, Larre P, *et al.*: **Zika virus infection complicated by Guillain-Barre syndrome—case report, French Polynesia, December 2013.** *Euro Surveill.* 2014; **19**(9): pii: 20720.
[PubMed Abstract](#) | [Publisher Full Text](#)
 121. Rozé B, Najioullah F, Fergé JL, *et al.*: **Zika virus detection in urine from patients with Guillain-Barré syndrome on Martinique, January 2016.** *Euro Surveill.* 2016; **21**(9): 30154.
[PubMed Abstract](#) | [Publisher Full Text](#)
 122. Thomas DL, Sharp TM, Torres J, *et al.*: **Local Transmission of Zika Virus—Puerto Rico, November 23, 2015-January 28, 2016.** *MMWR Morb Mortal Wkly Rep.* 2016; **65**(6): 154–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 123. Cao-Lormeau VM, Blake A, Mons S, *et al.*: **Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study.** *Lancet.* 2016; **387**(10027): 1531–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 124. Morrison TE, Diamond MS: **Animal Models of Zika Virus Infection, Pathogenesis, and Immunity.** *J Virol.* 2017; **91**(8): pii: e00009-17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 125. Akl EA, Meerpohl JJ, Elliott J, *et al.*: **Living systematic reviews: 4. Living guideline recommendations.** *J Clin Epidemiol.* 2017; **91**: 47–53.
[PubMed Abstract](#) | [Publisher Full Text](#)

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Current Referee Status:



Version 1

Referee Report 10 December 2018

<https://doi.org/10.5256/f1000research.14886.r31780>



Alfonso Rodriguez-Morales 

Faculty of Health Sciences, Universidad Tecnológica de Pereira, Pereira, Colombia

Certainly, a systematic review (SR) on a such highly relevant topic, as Zika association with congenital brain abnormalities and Guillain-Barré syndrome. However, I should suggest first, to include other Zika congenital associated abnormalities, as we have the congenital Zika syndrome (CZS) but also extra-Central Nervous System (CNS) abnormalities.

The idea to have a living SR is excellent, however very compromising. Right now, this first version, requires urgently to be updated. As the date of update was till January 2017, as a first update.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Referee Expertise: Arboviral Diseases

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 03 July 2018

<https://doi.org/10.5256/f1000research.14886.r34944>



Hugh J. Willison 

Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, UK

This is a systematic review looking at the strength of evidence supporting the link between Zika virus (ZIKV) infection and neurological complications. The intention is to create a living review that is constantly updated as new publications arise, allowing researchers access to a data resource that keeps pace with the rapidly advancing evidence in the field. This is an extremely important initiative if it can provide truly up to date (i.e. as fast as a pubmed or similar search) and appropriately sifted information for those wishing to conduct spot checks on the current status of neuro-ZIKV.

From an aspirational perspective I support it strongly, but does it work in practice? Setting aside many complex methodological considerations that this article raises, how useful is such a resource and who is it there to serve? We would all welcome tailor-made and up-to-date information at our fingertips to help navigate the mountain and minefield of information on ZIKV. I suspect that whilst this review will be widely consulted by those interested in neuro-ZIKV, from policy-makers to researchers, we will still refer back to primary publication for detailed up-to-date information in our specialist areas. At least it will provide a generic overview that facilitates more in depth access to and analysis of the primary data.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 04 May 2018

<https://doi.org/10.5256/f1000research.14886.r33196>



Katrina J. Sullivan

Clinical epidemiology program, Ottawa Hospital Research Institute, Ottawa, ON, Canada

This systematic review assessed the causality of Zika virus in the development of congenital brain abnormalities and Guillain-Barre syndrome. To accomplish this, the 10 dimensions of casual associations were reviewed, and evidence obtained for each dimension were narratively reviewed. With the addition of 101 new studies, the authors were able to conclusively establish the causal association between Zika and adverse congenital outcomes. However, not all dimensions could be assessed concerning Guillain-Barre syndrome, even with the additional of new studies within this update. As a result, there is limited understanding within this field of research for Zika virus.

Thank you for allowing me to review this article. Overall it was well written, and did a good job addressing

all aspects of it's complex objective. Please find below my comments:

For the methods I would have liked to see more information. This review should be able to stand on it's own without the reader having to find the baseline review to find important methodological information:

1. I would have liked to see inclusion/exclusion criteria for the study (something that could easily be in a figure or table to save room).
2. Please include your search strategy as a supplementary file (just Embase would be sufficient). It sounds like a very simple search the way you've described it in the methods. Also would have liked more information about who designed the search (e.g. information specialist, librarian, the researchers) and if it was peer reviewed using PRESS. Finally, in the "analogy" section of the results you indicate this wasn't reviewed in the baseline review as the search strategy didn't include terms for it. This indicates to me that you must have updated your search between the baseline review and the update, but you don't say this in your methods.
3. There is no assessment for methodological quality, which you do address in your limitations. I think this is an important step when you're including different study designs (although can also be challenging for the same reason). Probably not appropriate to give the same weight to a case report as a cross-sectional study, or an animal experiment and an epidemiological study.

General:

1. I find Table 1 a bit difficult to read, maybe because instinctively I'd expect the column for "U1, N" to be the total number of studies in the update, rather than just the new studies added with this update. This only becomes obvious when you look at rows like "case series" and you see the U1 has less studies than BR. If you keep this structure, it would be nice to add another column that has total N (as it was the total N that you're drawing conclusion from, the BR and U1 don't stand alone).

Living Systematic Review:

- Do the authors provide a clear rationale for the living systematic review? *YES, it meets all criteria for doing a living systematic review (priority question for decision making, important level of uncertainty in the evidence, emerging evidence that will likely impact conclusions)*
- Do the authors clearly state how this will be maintained as a living systematic review? *Partly - While they detail the process of U1-U3, the time for search, between updates, etc. changes with each update (as they anticipate the technology getting better). Living systematic reviews require explicit decisions on how often searching, data extraction, analysis, etc. will be performed.*

I feel this review is premature in saying that it is transitioned to a living systematic review. The intention of the living systematic review is to provide the reader with up to date evidence so the lag between the search and publication is minimize. The authors even define a living systematic review as "a systematic review that is continually updated, incorporating relevant new evidence as it becomes available". The search for this study ended in January 2017, and technically is out of date even for a regular systematic review (which we try to publish within a year). The authors say that they plan to update the review twice per year with formal peer review updates, but if that was the case then another 2 reviews should have been done since this date. Additionally, they authors indicate that only module 1 and part of module 3 of their living systematic review automation were in place by December 2017, meaning this wasn't used for this update.

Figure 2 already looks to be out of date - in it they propose that U2 would be published by Feb 2018. If they were able to accomplish this then U2 might have been more appropriate to call a living systematic review (where search looks to be from Jan to Dec 2017, and publication is Feb 2018).

I think it would have been more appropriate to publish this as an update of the systematic review, publish a protocol for how they were going to transition to a living systematic review (where Figures 1 and 2 would be included), and then treat U2 as their 'baseline' living systematic review, at which point the "living" aspect of the review is turned on and updates are given every 6 months (as they proposed).

Do the authors provide a clear rationale for the Living Systematic Review?

Yes

Do the authors clearly state how this will be maintained as a Living Systematic Review?

Partly

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Partly

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Referee Expertise: Systematic reviews, living systematic reviews

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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